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Letrozole treatment of precocious puberty in girls with the McCune-Albright syndrome; a pilot study*

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Context: Girls with McCune-Albright syndrome (MAS) and related disorders have gonadotropin-independent precocious puberty due to estrogen secretion from ovarian cysts. Their puberty does not respond to GnRH agonist therapy, and short-acting aromatase inhibitors have had limited effectiveness.

Objective: Our objective was to assess the effectiveness of the potent, 3rd generation aromatase inhibitor letrozole in decreasing pubertal progression in girls with MAS, and to assess the response of indices of bone turnover associated with the patients' polyostotic fibrous dysplasia.

Design: Subjects were evaluated at baseline, and every 6 mo for 12-36 mo while on treatment with letrozole 1.5 - 2.0 mg /M^2/d.

Setting: An open-label therapeutic trial at a single clinical center.

Patients: Nine girls age 3 – 8 yr with MAS and/or gonadotropin-independent puberty.

Main outcome measures: Rates of linear growth, bone age (BA) advance (BA/CA), mean ovarian volume (MOV), E, episodes of vaginal bleeding, and levels of the indices of bone metabolism: serum osteocalcin (OC) and alkaline phosphatase (AP), urinary hydroxyproline (OHP), pyridinoline (PYR), deoxypyridinoline (dPYR) and N telopeptides (NTP).

Results: Girls had decreased rates of growth ($P \leq 0.01$) and bone age advance (BA/CA, $P \leq 0.004$), and cessation or slowing in their rates of bleeding over 12 - 36 mo of therapy. MOV, E and indices of bone metabolism fell after 6 mo ($P \leq 0.05$), but tended to rise by 24 - 36 mo. Uterine volumes did not change. One girl had a ruptured ovarian cyst after 2 yr of treatment.

Conclusions: This preliminary study suggests that Letrozole may be effective therapy in some girls with MAS and/or gonadotropin-independent precocious puberty. Possible adverse effects include ovarian enlargement and cyst formation. (Clinicaltrials.gov number, NCT00006174)

Introduction

Precocious puberty and vaginal bleeding are often the presenting signs in young girls affected with the rare condition, McCune-Albright syndrome (MAS: the triad of precocious puberty and other forms of endocrine hyperfunction, cafe-au-lait pigment, and the bone disease, polyostotic fibrous dysplasia [PFD: OM#174800]). MAS is a sporadic disorder associated with postzygotic activating missense mutations (Cys or His → Arg ^{201}) in the gene for the α subunit of the stimulatory G protein (Gs α) that regulates cell function by coupling hormone and other receptors to adenylyl cyclase[i]. The mutations in MAS are often found in affected tissues, including the ovaries and bone lesions, and are sometimes also found in peripheral lymphocytes[ii]. The precocious puberty in MAS is caused by estrogen production from large ovarian cysts. In most girls, ovarian cyst formation appears to be independent of gonadotropin action; the gonadotropin levels are often low or in the prepubertal range, thus, the precocious puberty is gonadotropin-independent, and typically does not initially respond to treatment with the long-acting GnRH agonists[iii]. Surgical cystectomy or ovariectomy is almost always ineffective in girls with MAS because cysts usually develop in the remaining ovarian tissue[iv]. Adult stature in MAS patients with precocious puberty is often markedly decreased due to the combined factors of early fusion of the epiphyseal growth regions in the long bones (a result of elevated sex steroid levels) together with the deformities and fractures of the long bones caused by the PFD[v].

In MAS patients, the PFD exhibits a broad spectrum of severity, ranging from the presence of isolated lesions in the skull and/or extremities to involvement of the entire skeleton. In PFD, areas of normal bone and bone marrow are replaced by haphazardly-distributed regions of fibrous tissue intermingled by irregular trabeculae of woven bone[vi] resulting in skull and facial deformity, limb asymmetry, fractures and general disability. The condition is usually progressive over time, with enlargement of lesions and involvement of additional bones; the incidence of fractures is greatest in childhood, between the age of 6-10 y [vii]. The PFD is often associated with increased serum and urine levels of bone biomarkers (indices of bone metabolism) such as serum alkaline phosphatase (AP), serum osteocalcin (OC), and 24-h urinary levels of hydroxyproline (OHP), n-telopeptides (NTX), pyridinoline (PYR) and deoxypyridinoline (dPYR)[viii]. The levels of biomarkers often correlate with the extent and severity of skeletal involvement and with the degree of impairment of physical function in MAS[ix]. Patients may also exhibit renal phosphate wasting with a decrease in the renal tubular maximum reabsorption of phosphate relative to glomerular filtration rate (TmP/GFR). This may result in low levels of serum phosphate[x], with hypophosphatemic rickets and lesional osteomalacia that may exacerbate the deformities of the bone disease.

It is not known whether exposure to elevated levels of sex steroids directly affects the progression of bone lesions in MAS patients. Estrogen receptors have been identified in a bone lesion from a pregnant woman with MAS[xi] and increased levels of bone biomarkers have been observed during pregnancy in MAS patients[xii] suggesting that estrogens or other intrapartum growth factors could stimulate lesion growth. In addition, we have

observed that girls who present with vaginal bleeding and precocious puberty at a very early age (<1-2yr) often have severe, progressive, disabling FD as well, although it is also possible that this reflects the presence of a higher concentration of mutated cells in the ovaries, bones and other organs of severely affected subjects.

Establishing a safe, effective, long-term treatment for the precocious puberty in girls with MAS, and in girls with isolated gonadotropin-independent precocious puberty without the other signs of MAS, has been a challenge. Trials have studied drugs that block the biosynthesis of estrogens, such as the aromatase inhibitors, and estrogen antagonists. Our own early studies demonstrated that the short-acting aromatase inhibitor testolactone (Teslac) was partially effective therapy initially, but that puberty resumed in many girls after 2-4 yr of treatment[4]. Conversely, our studies of the second generation, non-steroidal aromatase inhibitor fadrozole, used together with a GnRH agonist, demonstrated no benefit in a group of girls with MAS[xiii].

A recent 12-month trial of the estrogen antagonist Tamoxifen in 25 girls with MAS has yielded promising initial results, with decreased mean rates of linear growth, bone age advance and vaginal bleeding[xiv]. However, no information is available at the present time regarding tamoxifen's effectiveness beyond 12 months of therapy, and the finding of an increase in average uterine volumes during treatment raises concerns that tamoxifen may have adverse effects on the endometrial stroma.

The potent, long-lasting aromatase inhibitor letrozole (Femara ™, Novartis Pharmaceuticals) is now used for the treatment of estrogen-dependent malignancies such as breast cancer. Letrozole reportedly suppresses estrogen levels by > 95% in postmenopausal women, and is usually administered at a dose of 2.5 mg (~1.5 mg/M^2)/day. It has not been associated with clinical evidence of impaired biosynthesis of aldosterone or cortisol[xv]. Side effects in adult women have reportedly included musculoskeletal discomfort (22%) and nausea (15%)[xvi].

Here, we report the results of a study designed to assess the effectiveness of letrozole in treating the precocious puberty in girls with MAS, and to learn whether treatment would affect the serum and urine levels of the indices of bone metabolism that reflect the activity of PFD[xvii].

Subjects and methods

Subjects (Table 1)

The subjects were 9 girls with gonadotropin-independent precocious puberty who had initially presented at ages 1.3 – 6.0 y with breast development, vaginal bleeding or discharge, and suppressed levels of LH and FSH. All girls had advanced BA and 8 had significantly increased growth rate SDS scores. Seven girls had areas of *cafe-au-lait* pigment. No girl had the thyroid abnormalities (suppressed TSH, elevated T3 or thyroid inhomogeneity on ultrasound) characteristic of many patients with MAS, and none had a history of adrenal hyperfunction. Serum phosphate levels were normal for age (4.5 - 5.6

mg/dL) in all girls. ^{99}Technetium bone scans and/or skeletal survey revealed asymmetrical areas of increased uptake and ground glass lucencies in the skull and /or extremities in 5 girls , indicating the presence of active PFD. Patient #2 had sustained a fracture of the R femur at age 3.8 y and also had a moderate scoliosis (37°) at the start of therapy. Patient #2 had also been treated with testolactone, 40 mg/kg/d, with inadequate response. Her testolactone was discontinued 6 mo prior to initiating letrozole. Patient 6 had a fracture of the L femur at 3 yr, that was treated with an intramedullary rod. Patient #3 had undergone R ovariectomy at age 1.3 yr, and patient # 8, a R ovarian cystectomy at age 2.0 yr; pubertal development and vaginal bleeding recurred in both these girls. Patient #9 had gonadotropin-independent puberty and bleeding at age 6 yr, but had no other skin or bone signs of MAS.

Methods

Protocol

Following a 3-6 mo baseline period, Letrozole was initiated orally at a dose of 0.5 mg/m^2/d during days 1-7 of treatment. The dose was increased to 1.0 mg/m^2/d on days 8-14 and to 1.5 mg/m^2/d on days 15-21. There was an option to increase the dose to 2 mg/M^2/d during therapy if a patient had progressive bone age advance, elevated serum estradiol levels or increased ovarian cyst volume while on 1.5 mg/M^2/d. The dose was divided bid (q 12 h) to decrease the possibility of gastric discomfort.

At the start of the study, to confirm the effectiveness and the safety of letrozole, the first 4 subjects (patients #1-4) were treated for 6 mo, followed by a 6 mo withdrawal period (Table 2). These subjects were evaluated every 3 mo during the on and the off treatment periods. On the last day of the 6-mo on-treatment period, serum levels of letrozole were measured at 0, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 24h after the final, am dose of drug.

In these 4 subjects, Letrozole was re-started following the 6 mo off-treatment period when girls exhibited recurrent signs and symptoms of puberty (vaginal bleeding, breast development &/or BA progression).

Because the safety and apparent effectiveness of letrozole had been confirmed by the initial studies in patients 1-4, patients 5-9 were given uninterrupted therapy for periods of 12 – 36 mo. These patients were evaluated every 6 mo. In patients 1 – 4, the 12, 24 and 36 mo data were obtained from the periods of continuous, uninterrupted letrozole therapy that was begun following the completion of the initial 6 mo on/6 mo off periods. Patients 1, 3 & 4 received 36 mo, and patient 2 received 12 mo of uninterrupted treatment.

The patients' mean ovarian volume (MOV), E, LH and FSH and indices of bone turnover values are presented at baseline (before treatment), 6 mo following the start of treatment, and after 12 , 24 and 36 mo of uninterrupted treatment. The linear growth and BA/CA values are presented after 12, 24 and 36 mo of uninterrupted treatment.

Growth, ovarian volume, skeletal maturation

Height was determined at 0900 as the average of 3 measurements on a stadiometer. Growth rate (cm/yr) was expressed as standard deviation units (standard deviation score; SDS) compared to normal girls of comparable age. Ovarian volumes were calculated using pelvic ultrasonography according to the formula: volume = length x width x thickness x 0.52[xviii] The MOV denotes the mean of the volume of the right and left ovaries. When one ovary was absent, the MOV was the volume of the remaining ovary. Uterine length was estimated from the craniocaudad dimensions of the uteri. Bone age was determined according to the method of Greulich and Pyle[xix]; all bone ages were read by a single investigator (SH) who was blinded to treatment status. Frequency and duration of vaginal bleeding were obtained from parental diaries, and recorded as days/episodes of bleeding in each 6 mo period.

Serum and urinary assays

Blood samples were collected at 0900 after an overnight fast. Urine measurements were performed on aliquots from 24-h collections collected coincidentally with serum. Commercial immunoassay kits were used to measure levels of estradiol (E, Diagnostic Products Corp), LH and FSH (Abbott Laboratories) and Osteocalcin (OC , Immunoradiometric assay, Nichols Institute Diagnostics). Urinary hydroxyproline (OHP) and pyridinoline-deoxypyridinoline (PYR; dPYR) were measured using a commercial HPLC, and urinary n-telopeptides (NTX) were measured using a commercial immunoassay (Mayo Medical Laboratories).

Renal phosphate handling (TmP/GFR)was measured with aliquots from 24 h urine collections as previously described using an adaptation of the nomogram of Bijvoet[xx].

Serum concentrations of letrozole were measured by HPLC following extraction using previously described methods.[xxi] The detection limit of the assay was 1.4 nmol/L and the interassay coefficient of variation was 9.8%.

An Institutional Review Board at the National Institutes of Health approved the protocol, and informed consent was obtained from a parent.

Results

Initial 6 mo trial (Patients 1-4; Table 2)

During the 6 mo on treatment, the mean ± SD MOV, ΔBA/ΔCA and growth velocity SDS were decreased compared to before treatment. E fell during therapy (213 vs < 20 pg/mL) in patient #2, the only subject with detectable serum E at the start of therapy. During the 6 mo off letrozole, the mean MOV, ΔBA/ΔCA and growth SDS increased in all girls.

Patients 3 and 4 had no vaginal bleeding during treatment, patient 1 had a single episode 1 mo after starting treatment, and patient 2 continued to bleed, but at a decreased frequency. Patients 1 and 4 had a decrease in breast stage, and patients 2 & 3 had a decrease in pubic hair stage after 6 mo of treatment.

During the 6 mo of letrozole treatment, there were significant decreases in the mean ± SD levels of the serum markers of bone formation AP and OC ($P<0.05$ compared to before treatment). There were also decreases in the urinary marker of bone resorption OHP ($p<0.05$ compared to before treatment) and decreasing trends in the mean levels of NTX, dPYR and PYR, although these latter changes were not statistically significant. During the 6 mo off therapy, the urinary indices of bone turnover rose toward pretreatment levels.

The mean ± SD TmP/GFR was within the previously-reported normal range (3.5 - 7.3 mg/100mL for children 2- 15y [3]) at baseline, and did not change during letrozole treatment (before treatment, 4.8 ± 0.4 ; during treatment, 4.4 ± 0.4 mg/100mL). The serum phosphate levels, random serum cortisol and plasma renin activity levels remained normal in all girls throughout the study. Letrozole was restarted in subjects 1-4 after completion of the 6 mo off-treatment period, and was continued without interruption for 12 – 48 mo. The clinical and laboratory values during long-term treatment in these subjects (see below) is from observations obtained after 12, 24 and 36 mo of uninterrupted letrozole.

Long-term studies

Growth and pubertal changes (Fig I).

The subjects' mean ± SD BA/CA and growth velocity SDS were significantly decreased after 12, 24 and 36 mo treatment compared to before therapy. The mean serum E and MOV fell markedly at 6 mo, but tended to increase toward baseline levels by 12 and 24 mo, however, these changes did not achieve statistical significance due to marked variability in parameter values. Notably, at 24 mo, the mean MOV tended to be higher than before the start of therapy due to an increase in ovarian cyst volumes in some girls. The patients' mean baseline LH remained at or less than the assay detection limit (1.0 mIU/mL) both before and at all time points during treatment. The mean baseline FSH was low before treatment, but tended to rise during therapy (1.5 ± 1.3, 2.2 ± 1.6, 2.4 ± 1.9 , 1.9 ± 1.2 and 3.0 ± 2.5 mIU/mL before, and at 6, 12, 24 and 36 mo, respectively).

Uterine size did not change significantly during letrozole treatment (mean ± SD craniocaudad uterine length was 4.3 ± 0.9, 3.8 ± 0.8, 4.6 ± 1.4, 4.8 ± 1.0 , and 4.3± 0.4 cm at 0, 6, 12 , 24 and 36 mo, respectively.)

Vaginal bleeding and pubertal staging

Of the girls who had vaginal bleeding before therapy, patients 4-9 had no more bleeding , Patients 1, 2 & 3 had a decrease in frequency (pt 2) or 1 episode of spotting per year (Pts 1 & 3) during the 12- 36 months of letrozole treatment. Pubertal stages of

breasts and pubic hair stabilized (II-IV and I-IV, respectively, before therapy, vs II-V and I-V after 12-36 mos of letrozole).

Indices of bone turnover (Fig 2)

The mean serum OC and AP , and the mean OHP fell after 6 mo of treatment, but rose at 12 and 24 mo toward the pretreatment levels. Levels of NTX, PYR and dPYR also tended to decrease at 6 mo, but these changes were not statistically significant.

Serum letrozole levels

Letrozole was detectable in serum in patients 1-4 at all time points between 0 and 24h after the final am dose of drug. Mean ± SD serum levels were 188 ± 107 [range 104-296] at 3h, and 178 ± 53[range 148 - 257] nmol/L at 24h, which is consistent with the long 1/2 life (approximately 2d) previously reported for adult subjects. However, the levels in our patients were only 25% - 67% of the steady-state levels in adult women age 52-76y (Mean 467 ± 52 nmol/L) who were treated for 8 weeks at a dose of 2.5 mg/d.[xxii]

Serum levels in Patient #2, who had continued to have vaginal bleeding, although less frequently than before therapy, were not lower (3h, 167 nmol/L; 24 h, 158 nmol/L) than those in the other 3 girls, who had stopped bleeding while on treatment

Adverse effects during treatment

Patient #1 complained of nonspecific discomfort in the hands and feet during the first 1-2 mo of treatment; this resolved spontaneously. Patients #3 & 6 reported transient episodes of abdominal pain, nausea and vomiting associated with viral syndromes, these episodes also resolved spontaneously. Patient #4, had a mild elevation of total serum bilirubin (1.1 – 1.4 mg/dL) during and following discontinuation of letrozole, which was restarted at a reduced dose (1.0 mg/M^2/d) as a precautionary measure.

Patient #7 developed acute abdominal pain and vomiting after 28 mo of letrozole treatment and 4 months after her dose had been increased to 2 mg/M^2/d due to ovarian enlargement. A right - sided hemorrhagic ovarian cyst was identified, with evidence of ovarian torsion. The cyst was removed via laparoscopic surgery. Letrozole was discontinued immediately. A GnRH stimulation test performed at a subsequent evaluation in the study clinic indicated that her gonadotropins had entered the range of central puberty (baseline and 120 min LH and FSH: 5 and 95 : 3 and 21 mIU/mL, respectively), hence she was started on GnRH agonist treatment with good response.

Two patients with more advanced PFD had progression of their bone disorder during therapy: In patient #2, a thoracolumbar scoliosis progressed (37° $\rightarrow$ 42 °) over the 12 mo of treatment, and patient #6 sustained increased leg asymmetry and fractures of the humerus and of the 5^{th} finger after 18 mo of treatment. These are expected complications of PFD in MAS children.

Discussion

This pilot study of 9 girls with MAS indicates that letrozole can be effective treatment for girls with gonadotropin-independent precocious puberty. Our patients had decreased rates of growth and bone maturation, and cessation or slowing of menses during therapy. However, although there was a significant decrease in ovarian volumes over the first 6 mo, the mean MOV tended to increase over the 1st and 2nd years of treatment, and cysts redeveloped in some girls.

Because MAS is a rare disorder, and because data from an untreated control group of subjects were not available, we designed the study so that each girl would serve as her own control. In subjects 1-4, 6 mo baseline data was compared with 6 mo on letrozole treatment, and with 6 mo off treatment. Subjects 5-9 were given uninterrupted letrozole and the results compared to baseline data for each subject. Because the number of subjects was small in this preliminary study, and the experimental design not optimal, a larger number of subjects must be enrolled and treatment continued for a longer time in order to confirm the effectiveness of letrozole treatment on precocious puberty in girls with MAS and similar disorders, and to establish its long-term effects on indices of bone metabolism.

We found that serum concentrations of letrozole in our patients were only 25- 67% of the mean steady-state plasma levels previously reported in older, postmenopausal women who were given comparable doses. It is possible that our young subjects had a more rapid drug clearance rate, but because we did not measure serum metabolites or urine

concentrations, and did not measure serum concentrations beyond 24h, we are not able to better characterize the pharmacokinetic disposition of letrozole in our patients. Although the individual patients' levels exhibited variability over the period of sampling, our finding that mean levels declined by only 5 % over 24h indicates that a single, daily dosing schedule would be appropriate for young children. We found that letrozole concentrations in the patients who stopped menstruating entirely, and thus appeared to respond better to treatment, were not higher than in the 2 who had some persistence of menstrual bleeding.

In normal girls, markers of osteoblastic bone formation (serum OC and AP) and of bone and collagen resorption (urinary OHP, PYR and dPR) increase as girls progress from pubertal stages Tanner I to III, then decline to adult levels by Tanner stages IV & V. Levels of these biomarkers tend to parallel the rates of linear growth that accompany the advent of puberty.[xxiii xxiv xxv] Bone biomarker levels are often markedly increased in patients with fibrous dysplasia [8 xxvi xxvii], and can fall following treatments that slow rates of bone turnover. We observed a decrease both in markers of bone formation and of bone resorption after the first 6 months of letrozole treatment,. We propose that this could have been an initial response to the decreased estrogen levels and a slowing of puberty in these patients, although we are not able to rule out a direct suppressive effect of letrozole on the activity of osteoblast/osteoclast units. However, bone biomarker levels in our subjects returned to pretreatment levels after 12 -36 mo of letrozole, suggesting that a decrease in estradiol levels may not have long-term suppressive effects on the activity and growth of fibrodysplastic lesions. An additional factor is that the

small group of subjects in this pilot study presented with a relatively mild form of PFD; none had extensive, severe skeletal involvement, rickets, hypophosphatemia, or the markedly elevated levels of bone biomarkers that may be observed in MAS subjects. Continuing studies that include a greater number of girls with extensive PFD lesions may reveal whether the use of potent aromatase inhibitors can modify the progression of the bone disease.

Notably, one of our girls developed a large, unilateral ovarian cyst with ovarian torsion that necessitated surgical intervention. It is not certain that letrozole was directly responsible for this event, since ovarian cyst formation is a known complication of MAS in both pediatric and adult females. In this patient's case, several factors may have contributed to the severity of ovarian cyst enlargement: Her subsequent increased gonadotropin responses after GnRH stimulation indicated that she had rapidly developed gonadotropin-dependent puberty during her 3rd year of letrozole therapy, between her study evaluations. This may have been related to her increased letrozole dose (2 mg/M^2/d). Studies in adults have shown that higher doses of letrozole (2.5 – 5.0 mg/d) and anastrozole are effective adjunctive treatments in the stimulation of gonadotropin release, follicle enlargement, and in inducing ovulation in women undergoing fertility treatments[xxviii xxix].

We were not able to determine the underlying cause of the hand/foot discomfort in patient #1. Her laboratory studies were unremarkable, and neither the bone scan nor X

ray studies revealed significant fibrous dysplasia at these sites. This finding may reflect the musculoskeletal complaints reported by adult women treated with letrozole.

This preliminary study indicates that letrozole can be an effective initial treatment for girls with gonadotropin-independent precocious puberty, and may also offer an alternative therapy for girls who fail to respond to blockers of estrogen action such as tamoxifen. A greater number of subjects and longer periods of treatment are needed before the safety and effectiveness of letrozole can be confirmed. Importantly, the present study indicates that ovarian enlargement and recurrent cyst formation may occur during therapy, particularly in girls receiving higher doses of drug. Patients should be observed at intervals of 3-6 mo during treatment, and gonadotropin levels measured to rule out the onset of central puberty.

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Figure Legends, Feuillan *et.al*

Fig 1: Mean ± SD growth rate SDS, BA/CA, mean ovarian volume (MOV) and serum estradiol (E) in girls with MAS before treatment 0 mos (9 pts) and at 6, 12 (9 pts), 24 (7pts) and 36 (5 pts) mo of letrozole therapy. *, $P \leq 0.01$; **, $P \leq 0.004$.

Fig 2: Mean ± SD serum osteocalcin (OC), alkaline phosphatase (AP) , and 24 h urinary hydroxyproline (OHP), pyridinoline (PYR), deoxypyridinoline (dPYR) and N telopeptides (NTP) in girls with MAS before treatment 0 mos (9 pts) and at 12 (9 pts), 24 (7pts) and 36 (5 pts) mo of letrozole therapy. *, $P \leq 0.05$ [Normal ranges in prepubertal children: OC, 40.2 – 108 ng/mL; AP, 115-303 u/L; OHP, 100-150 μg/mg creat. PYR, 158 – 441 nmol/mmol creat.; dPYR, 31 – 112 nmol/mmol creat. ; NTP, 576 – 1763 nmol/mmol creat;]

Table 1: Clinical characteristics of 9 girls with MAS at the start of letrozole therapy.

Patient	CA (yr)	BA (yr) [BA/CA]	Height (cm) [SDS*]	Growth (cm/yr) [SDS*]	Pubertal stage Br/PH	*Café-au-Lait* pigment	Bone Disease[1]	Menses	Previous tx for puberty
1.	4.3	8.3 [1.9]	99.5 [-0.8]	13.2 [+5.0]	IV/I	Yes	++	Yes	None
2.	5.8	11.0 [1.9]	128.2 [+2.7]	9.9 [+3.8]	IV/II	Yes	+++	Yes	Testolactone
3.	4.8	8.3 [1.7]	108.4 [+0.4]	10.8 [+4.0]	IV/I	Yes	+	Yes	R ovari-ectomy
4.	5.9	8.8 [1.5]	119.8 [+1.1]	9.3 [+3.2]	IV/IV	Yes	+	Yes	None
5.	6.1	8.8 [1.4]	120.1 [+0.9]	10.6 [+4.6]	IV/III	Yes	No	No	None
6.	3.5	5.0 [1.4]	103.0 [+1.5]	11.0 [+2.7]	IV/I	Yes	+++	Yes	None
7.	4.8	10 [2.1]	116.8 [+2.4]	8.5 [+1.5]	IV/III	Yes	No	Yes	None
8.	3.3	6.8 [2.1]	105.0 [+2.3]	11.8 [+2.6]	IV/III	No	+	Yes	R ovarian cystectomy
9.	8.1	12.0 [1.5]	132.5 [+0.7]	6.3 [+0.6]	II/II	No	No	No	None

* Standard Deviation Score, compared to normal girls of comparable chronologic age.

[1] +: Mild, absence of facial asymmetry, limb length discrepancy or gait abnormality, ++: Moderate; facial or skull asymmetry, limb length discrepancy. No fracture or surgery, +++ Marked; as in Moderate, but impaired mobility, fracture, previous surgery.

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Table 2 Response to 6 mo trial of letrozole therapy in 4 girls with precocious puberty and polyostotic fibrous dysplasia of bone due to MAS. Results are the mean ± SD of observations at -3 and 0 mo prior to treatment (Before); +3 and +6 mo during treatment (During), and +9 and +12 mo after discontinuation of treatment (After).

	Before	During	After
MOV (mL)	5.3 ± 5.7	1.4 ± 1.0 *	4.3 ± 4.3
ΔBA/ΔCA	1.6 ± 0.3	1.5 ± 0.3 *	1.4 ± 0.3
Growth rate[SDS**]	2.8 ± 1.4	-1.2 ± 1.0	2.5 ± 3.5
Serum AP (U/L)	361 ± 72	275 ± 68 *	301 ± 69
OC (ug/L)	75 ± 23	54 ± 45	30 ± 3
Urine OHP (ug/mg Cr)	231 ± 51	147 ± 46 *	179 ±39
NTX(nmol/mmol Cr)	835 ± 227	570 ± 220	652 ± 181
dPYR (nmol/mmol Cr)	73 ± 13	65 ± 27	75 ± 20
PYR (nmol/mmol Creat)	306 ± 45	263 ± 96	305 ± 54

*: P< 0.05 compared to before treatment ** : Standard deviation score compared to normal girls of comparable age.
To convert E to pmol/L, multiply by 3.671; to convert OC to nmol/L, multiply by 0.17; to convert OHP to mmol/mmol Creat multiply by 0.86.

Figure I.

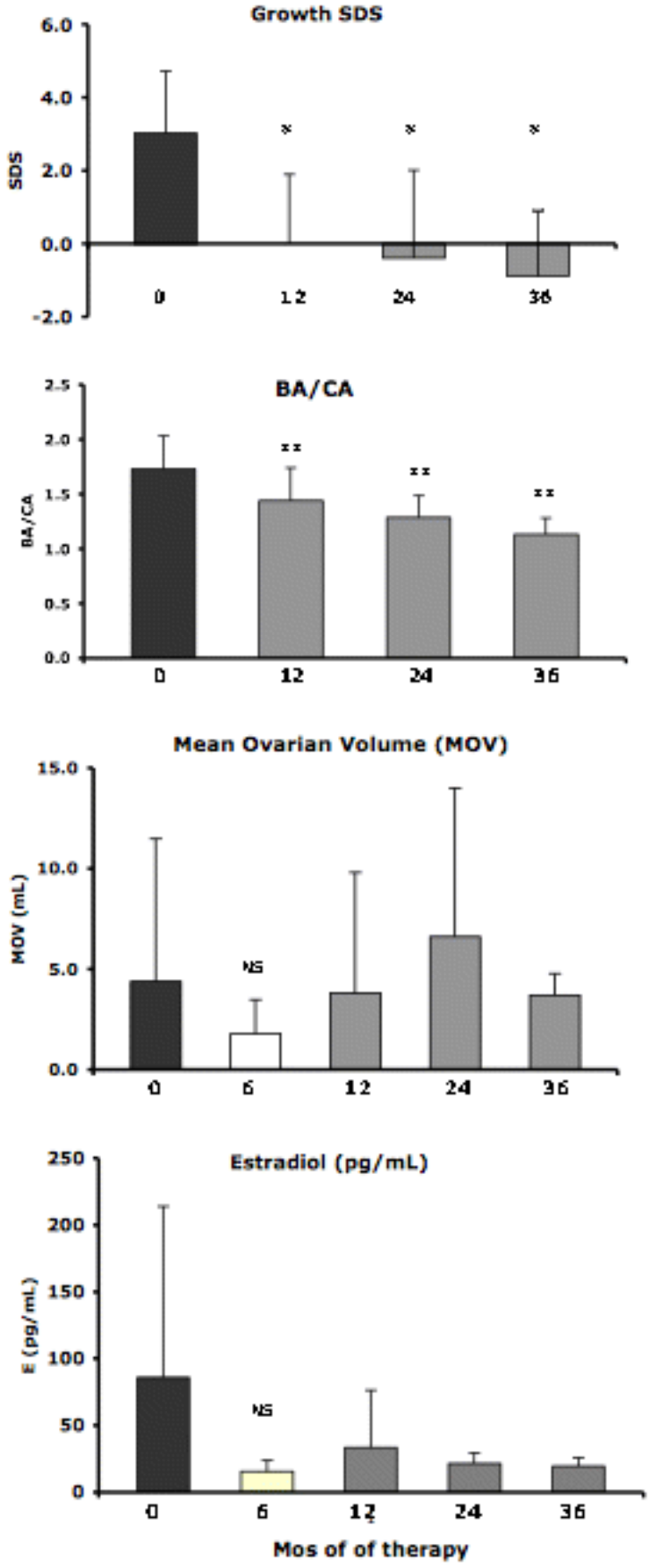
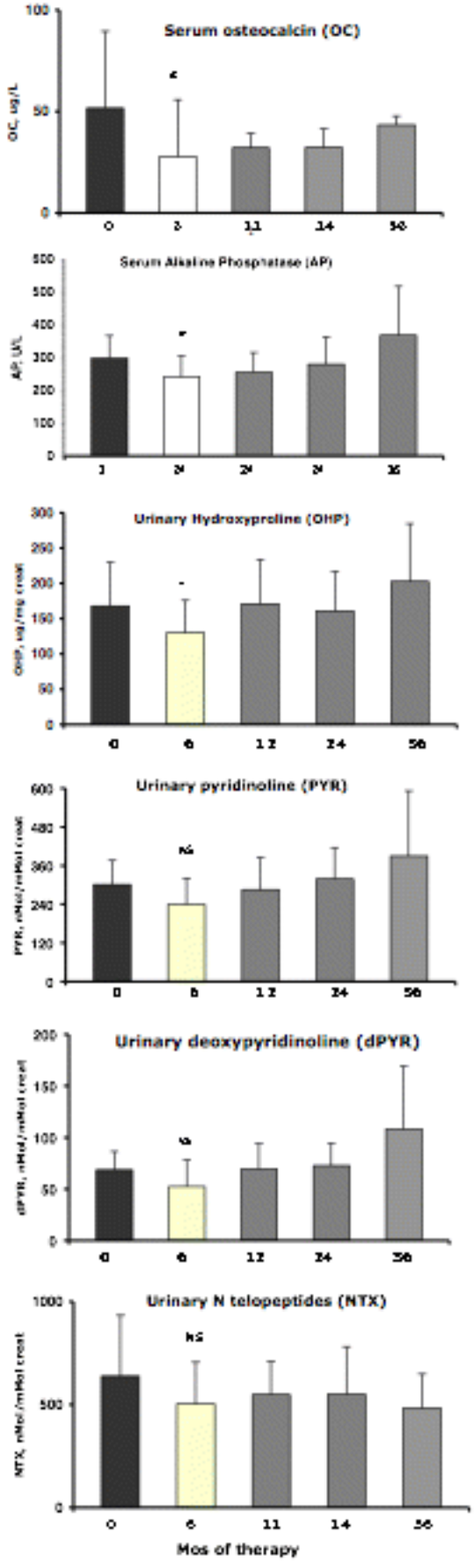

Growth SDS
SDS
6.0
4.0
2.0
0.0
-2.0
0
12
24
36
*
*
*
BA/CA
BA/CA
2.5
2.0
1.5
1.0
0.5
0.0
0
12
24
36
**
**
**
Mean Ovarian Volume (MOV)
MOV (mL)
15.0
10.0
5.0
0.0
0
6
12
24
36
NS
Estradiol (pg/mL)
E (pg/mL)
250
200
150
100
50
0
0
6
12
24
36
NS
Mos of of therapy

Figure 2.


Serum osteocalcin (OC)
OC, ug/L
Serum Alkaline Phosphatase (AP)
AP, U/L
Urinary Hydroxyproline (OHP)
Urinary pyridinoline (PYR)
Urinary deoxypyridinoline (dPYR)
Urinary N telopeptides (NTX)
NTX, nMol/mMol creat
Mos of therapy